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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/172,799	08/13/98	SCHOENROCK	BERLIOR-5

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EXAMINER	
BORIN, M	
ART UNIT	PAPER NUMBER
1631	18

DATE MAILED: 02/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/132,799	Schoenrock et al.
Examiner	**Group Art Unit**
Michael Borin	1631

Responsive to communication(s) filed on _____.

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1 and 3-13* is/are pending in the application.

Of the above, claim(s) *5, 7-10, and 13* is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1, 3, 4, 6, 11, and 12* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 11/21/2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/132799 is acceptable and a CPA has been established. An action on the CPA follows.

Status of claims

2. Claims 1,3-13 are pending.

In response to restriction requirement made in the course of prosecution of the parent case, applicant elected Group I, claims 1,3-6. Accounting for claim amendments, the Group now includes claims 1,3,4,6,11,12. Claims 7-10,13 remain withdrawn from consideration as being drawn to non-elected group.

Applicant notes that the election has been done with traverse. The traverse was addressed in the Office action mailed 03/13/00 (paper #9).

As per election of species, the species monomer oligopeptide species of example 4 (Ac-VVRP-NH_2 ;p. 37) remain under consideration. Claims reading on the elected species, 1,3,4,6,11,12 are examined on merits to the extent they read on the monomer oligopeptide VVRP, its amide and or N-acetyl derivative. Claim 5 remains withdrawn from consideration as being drawn to non-elected species.

Claim Rejections - 35 U.S.C. § 102 and 103.

3. Claims 1, 3 remain rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al (Agric. Biol. Chem., 54, 835-836, 1990).

The instant claims, in part defined in claim 1, items (1) and (3), are drawn to water-in-oil preparations comprising peptide VVRP, or peptides comprising said sequence VVRP.

Kohmura

Kohmura et al. describe fragments of human κ casein, in particular peptide having sequence VVRP (i.e., a peptide of the instant invention). See p. 835, Table 1, compound No. 6. Further, the reference teaches peptides comprising said sequence VVRP: AVVRP, PAVVRP, NPAVVRP, ANPAVVRP, YANPAVVRP (i.e., peptides as instantly claimed, wherein $\psi = 1 \div 5$, $\Omega = 0$). See p. 835, Table 1, compounds No. 7-11. The referenced peptides exhibit a strong inhibitory effect on angiotensin-converting enzyme (ACE), the latter being an important regulator of blood pressure (see, e.g., p.835, second column). Kohmura does not teach administration of the referenced peptides in a form of pharmaceutical composition.

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to prepare a pharmaceutical composition comprising peptides of Kohmura as an active ingredient, because Kohmura teaches that these peptides inhibit ACE activity and, therefore, may be useful in treatment of ACE-mediated processes, such as regulation of blood pressure. Further, the courts held that it is well known without citation of authority that drugs and pharmaceuticals are

usually dispensed in either liquid or solid carriers. One of primary skills in the art would have known that compound "X" would have had to be formulated in some manner so as to make it useful pharmaceutically. In re Rosicky, 125 USPQ 341 (CCPA 1960). Anyone would be capable of preparing a composition from a known compound. See, e.g., "Remington Pharmaceutical Sciences", part 8, Mack Publishing Co., Easton, PA, 1980. Further, in regard to water-in-oil form of composition, such form is customary for pharmaceutical compositions.

Applicant argues that Kohmura at best suggests that the referenced compounds are used in oral or parenteral formulation which are usually oil-in-water formulations. Moreover, applicant contends that "oral or parenteral compositions are never water-in-oil based formulations". Examiner respectfully disagrees. First, oral or parenteral formulation are not necessarily oil-in-water formulations. US 5,665,700 is cited to demonstrate that oral or parenteral formulations are used as water-in-oil formulations. Second, it is not clear why applicant assumes that ACE inhibitors should be used internally, not topically. US 5,346,887 is cited to demonstrate that ACE inhibitors are know to be used in formulations for topical administration.

4. Claims 1, 3 remain rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al, supra., and further in view of Atlas of Protein Sequence and Structure (Vol. 5, 1972). The rejection is maintained for the following reasons of record.

The instant claims, in part defined in claim 1, item (2), are drawn to compositions comprising oligopeptide VVRP wherein one of Val residues is replaced by leucine or isoleucine, or methionine

residues. It is well known that several amino acids are considered to conservative substitutions of Val. These amino acids include Leu, Ile and Met. Atlas of Protein Sequence and Structure, p. 96, is cited to show that such amino acids are known conservative substitutions of Val (see col. 8). Therefore, in view of the equivalence of Val, Ile, Leu, and Met, the use of Ile, Leu or Met amino acid residues in place of Val in the primary reference would have been obvious to one of ordinary skill in the art at the time the invention was made. One would expect, in the absence of evidence to the contrary, that peptides resulting from substitution of a Val residue in VVRP peptide taught in Kohmura with Ile, Leu, or Met residues will have similar biological activity and thus be also useful in pharmaceutical preparations.

5. Claims 1, 3, 4 remain rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al. supra., and further in view of Bundgaard (Design of Prodrugs, Chapter 1, 1985) and Sumner-Smith (US 5,646,120). The rejection is maintained for the following reasons of record.

The instant claims, in part defined in claim 1, items (5-7), are drawn to compositions comprising peptide comprising sequence VVRP peptide and having acetyl protective group at N-terminus and/or amido group at C-terminus.

The Kohmura reference is applied as above. It is well known in the peptide art to administer peptide in a form of their prodrugs which have protected N- and/or C- termini because such substitution allows to optimize their solubility and/or stability and make them more suitable for pharmaceutical applications. The most common prodrugs are those requiring a hydrolytic cleavage

mediated by enzymatic catalysis. See Bundgaard, p. 1. Sumner-Smith is cited to illustrate use of acetyl group to protect NH_2 terminal group, and amido-group, to protect COOH terminal group in peptides prepared for *in vivo* administration. See col. 2, lines 45-52,col. 6, lines 42-50, 53-62. Therefore, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to use peptides described by Kohmura in pharmaceutical compositions in a form of a prodrug analog having protected N- and/or C-termini with a reasonable expectation that such prodrugs will have at least similar effectiveness in inhibition of angiotensin-converting enzyme and regulation of related physiological processes.

6. Claims 1, 3 are rejected under 35 U.S.C. 103(a) as obvious over Steffens et al. (US Patent 5,681,721) in view of "Remington Pharmaceutical Sciences" and WPIDS abstract 1978-34432 (JP 53034915).

The instant claims, in part defined in claim 1, item (4), are drawn to compositions comprising protein with molecular weight of between approximately 0.5 and 100 kD, said protein comprising oligopeptide VVRP.

Proteins comprising sequence VVRP are well described in the prior art: Search in Registry file of STN Database produced 396 hits. Steffens et al reference is used as a representative.

Steffens

Steffens teaches bifunctional urokinase variants having improved fibrinolytic characteristics and thrombolytic pharmaceutical compositions comprising thereof. See claims 1, 18. In particular, the reference teaches protein

1 SKTCYEGNGH FYRGKASTDT MGRPCLPWNS ATVLQQTYHA HRSDALQLGL
51 GKHNYCRNPD NRRRPWCYVQ VGLKPLVQEC MVHDCADGKK PSSPPEELKF
101 QCGQKTLRPR FKIIGGEFTT IENQPWFAAI YRRHRGGSVT YVCGGSLISP
151 CWVISATHCF IDYPKKEDYI VYLGRSRLNS NTQGEMKFEV ENLILHKDYS
201 ADTLAHHNDI ALLKIRSKEG RCAQPSRTIQ TICLPSMYND PQFGTSCEIT
251 GFGKENSTDY LYPEQLKMTV VKLISHRECQ QPHYYGSEVT TKMLCAADPQ
301 WKTDSCQGDS GGPLVCSLQG RMTLTGIVSW GRGCALKDKP GVYTRVSHFL
351 PWIRSHTKEE NGLALSPVVV VVRPLGGGGN GDFEEIPEEY LQ

having VVRP moiety at positions 371-374 (underlined). See col. 11, compound M28.

The pharmaceutical composition of Steffens reads on the instantly claimed composition comprising peptides comprising VVRP sequence, except for the limitation "water-in-oil", added in the amended claim. Anyone would be capable of preparing a composition from a known compound and to select a proper formulation. See, e.g., "Remington Pharmaceutical Sciences", part 8, Mack Publishing Co., Easton, PA, 1980. Further, in regard to water-in-oil form of composition, such form is customary for pharmaceutical compositions. WPIDS abstract 1978-34432 (JP 53034915) is cited to illustrate use of water-in-oil formulation for intravenous injection of thrombolytic agents.

Applicant argues that composition of Steffens "appear to be injectable aqueous formulations" (emphasis added). First, the reference never stipulates that the referenced compounds must be injected strictly as aqueous formulations. Second, as now reflected in the rejection, injectable formulations can be in the water-in-oil form.

7. Claims 1, 3 are rejected under 35 U.S.C. 103(a) as obvious over Steffens et al., supra., and further in view of Atlas of Protein Sequence and Structure (Vol. 5, 1972). The rejection is maintained for the following reasons of record.

The instant claims, in part defined in claim 1, items (2), (4), are drawn to compositions comprising protein with molecular weight of between approximately 0.5 and 100 kD, said protein comprising oligopeptide VVRP wherein one of Val residues is replaced by leucine or isoleucine, or methionine residues. It is well known that several amino acids are considered to conservative substitutions of Val. These amino acids include Leu, Ile and Met. Atlas of Protein Sequence and Structure, p. 96, is cited to show that such amino acids are known conservative substitutions of Val (see col. 8). Therefore, in view of the equivalence of Val, Ile, Leu, and Met, the use of Ile, Leu or Met amino acid residues in place of Val in the primary reference would have been obvious to one of ordinary skill in the art at the time the invention was made. One would expect, in the absence of evidence to the contrary, that proteins resulting from substitution of a Val residue in VVRP moiety in the protein taught by Steffens with Ile, Leu, or Met residues will have similar biological activity.

8. Claims 1, 6,11,12 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al., supra, or Steffens et al., supra. The rejection is maintained for the following reasons of record

The instant claims are drawn to concentration range, 0.000001-10%, of compositions defined in claim 1.

The references are applied as above, see preceding paragraphs 6-10.

In regard to particular concentration ranges of the active ingredient in composition, Kohmura teaches that IC_{50} concentration of the referenced peptides is in the range 8-80μM, which corresponds to about 0.0005 - 0.005% (as compared to 0.000001 - 10% claimed range). Steffens et al use pharmaceutically effective concentrations (claim 18), which are presented in the reference in concentration units different from those instantly claimed. If there are any differences between Applicant's claimed preparations and that of the prior art, the differences would appear to be minor in nature. The instant invention's preparations, which fall within the scope of the prior art compositions, would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art at the time the invention was made because, in the absence of sufficient factual evidence or unexpected results to the contrary, Applicant's claims are directed to optimization of an "art recognized variable" which is well within the perview of one of ordinary skill in the art.

Conclusion.

9. No claims are allowed

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group

is (703) 305-3014. Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

May 21, 1999 MICHAEL E[illegible] PATENT [illegible]